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1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,314	NOBLE ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-23 and 38-53* is/are pending in the application.

4a) Of the above claim(s) *50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23, 38-49, 52-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

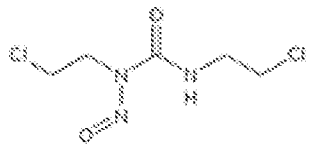
Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

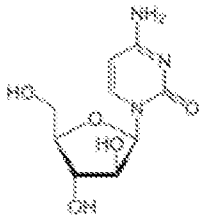
DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of acetyl-DEVD-aldehyde for the caspase inhibitor, carmustine (BCNU) for the non-caspase inhibitor, and vitamin C for the antioxidant in the reply filed on September 17, 2009 is acknowledged. The traversal is on the ground that there is no search burden for the non-elected genera. This is not found persuasive because the non-elected compounds have different functions and different chemical cores which require different search classifications which goes to burden. An example are the anticancer agents carmustine (BCNU) which is



which is classified as 514/589 and cytarabine which is



which is classified as 514/469 where there is a search burden evidenced by the different classifications.

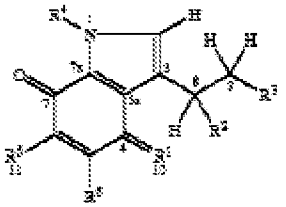
The requirement is still deemed proper and is therefore made FINAL.

Upon review of the claims and art, the composition consisting essentially of a caspase inhibitor and a composition comprising the combination of a agents for treatment are not viewed as distinct as Claim 18 allows for the inclusion of the other agents wherein it would not materially change the product as it would achieve the same purpose, unlike a claim that would recited “consisting of” a caspase inhibitor, wherein

the distinction between these claims are withdrawn but the election of the species is maintained.

The caspase inhibitor is expanded to include zVAD and the compounds of Gunasekera

Compounds of the subject invention can be represented by the following general formula:



wherein R^1 is NH or O;
R^2 is OZ;
R^3 is OZ;
R^4 is H or R;
R^5 is NH_2, NR_2, or OZ; and
R^6 is H or X;
wherein Z is selected from the group consisting of H, R, COR, mesyl, tosyl, glutamyl, succinyl, and malonyl;
R is selected from the group consisting of C1 to C8 alkyl, phenyl, and benzyl; and
X is Cl, Br, or I.

The non-caspase inhibitor is expanded to include etoposide and corticosteroids such as dexamethasone as the elected non-caspase inhibitor BCNU, is a caspase inhibitor as addressed with the 112 rejections below, and the election for the antioxidant is withdrawn.

Claims 50-51 are withdrawn.

Status of Application

2. The response filed March 7, 2009 and September 17, 2009 has been received, entered and carefully considered. The response affects the instant application accordingly:

a. Claims 13, 15-16, 18, have been amended.

b. Claim 1-12, 24-37 has been cancelled.

c. Claim 38-53 has been added.

3. Claims 13-23, 38-53 are pending in the case.

4. Claims 13-23, 38-49, 52-53 are present for examination.

5. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

6. All grounds not addressed in the action are withdrawn or moot.

7. New grounds of rejection are set forth in the current office action.

New Grounds of Rejection

Due to the amendment of the claims the new grounds of rejection are applied:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13-23, 44-49, 52-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a “caspase inhibitor”, an inhibitor that is a “pan caspase inhibitor”, an inhibitor “specific for caspase-3, caspase-8, or caspase -9”, and wherein the caspase inhibitor “inhibits the production of a caspase" or “inhibits the activation of a

caspase" or inhibits a signaling pathway of a caspase". The description is inadequate to one of skill in the art to distinguish what the inventors were in possession of at the time of filing.

First, claims and description define the caspase inhibitors and inhibitors specific for a particular caspase, by what it *does* and not *what it is.* Second, it does not describe adequately the degree of inhibition or specificity for the caspase of type of caspase that would fulfill the description. Third, there is no specific or clear structure function relationship for the compounds encompassed by the broad term.

As addressed in the specification (Page 11 lines 1-3) c-DEVD-CHO aldehyde inhibits caspase-3 preferentially but is not solely specific for caspase-3. As there is no adequate description as to the degree of preferential attachment for caspase-3 to be considered specific for the caspase, the fact pattern indicates that the artisan was not in possession of the claimed method of use. Additionally, Petak et al. (BCNU….) teaches that BCNU is both a caspase-mediated inhibitor and an anticancer agent. The specification however, addresses BCNU (carmustine) as an anti-cancer agent, not as a caspase inhibitor, which as taught by Petak, has the capacity to inhibit drug-induced apoptosis from etoposide at certain doses. As a result, there it is unclear what compounds are encompassed particularly in regards to BCNU which Applicant regards as a non-caspase inhibitor which as addressed by the instant specification (paragraph 44) **do not function as caspase inhibitors** which is repugnant to the art as *Petak shows BCNU to be as caspase inhibitor* and subject to the 112 2nd rejection below as the metes and bounds are unclear and goes to written description.

Specifically, BCNU is addressed as a species of alkylating agent to the broader grouping *of non-caspase inhibiting anti-cancer agents* which conflicts with the teachings of Petak where *BCNU is caspase-inhibiting*. The specification does not adequately disclose what is encompassed by the terms and the caspase inhibitors specifically recited in the specification are protein/peptide inhibitors and BCNU is a mustard derivative/alkylating agent. The disclosure does not clearly describe what the inventors were in possession of at the time of filing. As a result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

The scope of the terms are encompassing compounds yet to be discovered which are beyond Applicant's possession at the time of filing. As indicated by Okun et al. (Screening for Caspase-3 Inhibitors:…), caspases inhibitors, particularly caspase-3 inhibitors are an ongoing endeavor for pharmaceutical companies in a search for effective drugs. Okun teaches that screening methods were utilized to find caspase-3 inhibitors from their 650000 compound collection, where about 15000 potential inhibitors were subject to the screening against caspase-3 resulting in one particular compound (CD-001-0011)that was synthesized and tested for a class of double electrophillic warhead small-molecule inhibitors. *Okun teaches that the mechanism for susceptitibility of the caspase-3 is unclear and subject to speculation* (Discussion). As new caspase inhibitors are still being explored and the exact mechanisms for inhibitors are unclear, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

9. Claims 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims contain new matter. The claims recite acetyl-DEVD-aldehyde as a caspase inhibitor which is not described in the specification at the time of filing. There is support for acetyl-YVAD-aldehyde as it is the tetrapetide aldehyde Ac-YVAD-DHO and z-VAD-fluoromethylketone (zVAD.fmk), but there is no support for acetyl-DEVD-aldehyde in the instant disclosure. This is a new matter rejection.

10. Claims 45 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite mimetics, analogs, and polymers of the claimed antioxidants wherein there is no written description for the compounds encompassed by the recitation other than for those for superoxide dismutase as drawn in U.S. Pat. 5171680 cited in the specification. It is also noted for example, that selenium is an element wherein there is no description as to what would be a mimetic for an periodic element.

11. Claims 13-23, 38-49, 52-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the claimed

methods, and the art only provides enablement for (1) caspase inhibitors such as zVAD associated with PML protein and/or arsenic compounds for inducing and/or accelerated cell death for undesirable cells and/or with an agent inducing the overexpression of the PML protein such as interferon (Koken et al.); and (2) method of inhibiting cancer cell proliferation with certain aminoiminoquinone and aminoquinone alkaloid compounds that can be in combination with other agents (Gunasekera et al.-details addressed below). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method treating cancer with a caspase inhibitor, a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent, or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent and

an antioxidant. Thus, the claims taken together with the specification imply that every type of cancer such as colon, breast, brain, and lung; can be treated with either a caspase inhibitor, combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent, or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent and an antioxidant. The breadth of the claims is extremely broad to encompass millions of compounds and combinations to treat a wide variety of cancers with different states, organs, and etiology.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art and the unpredictability of the art in regards to the treatment of all cancers with a single agent or combination of agents is as follows:

The existence of such a "silver bullet" is contrary to our present understanding of oncology. Simone, Oncology: Introduction, *Cecil Textbook of Medicine,* 20th Edition, 1996 Vol. 1, pp.1004-1010, states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study' (see the enclosed article, page 1004). A 'disease caused by proliferation of tumor cell' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant.

Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held

insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against all cancers. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states, that "Treatment programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear. Similarly, Myelodysplastic syndrome (MDS) is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms and its incidence is unknown and further, there is no established treatment. Several growth factors and their receptors have been associated with glioma and the treatment depends on the pathology and location and is often multimodal.

Additionally, cell line data for cancer drugs is well-known to be unpredictive of treatment, even animal data is not predictive see Trisha Gura "CANCER MODELS: Systems for Identifying New Drugs Are Often Faulty" Science 7 November 1997: Vol. 278. no. 5340, pp. 1041 - 1042:

> "Indeed, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration. "The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all," says Alan Oliff, executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania."

The correlation between in vitro cancer models and clinical expectations has been summarized:

> "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation in vitro, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularization, perfusion and, thereby, drug access to the tumor cells are not evenly distributed and this fact consists an important source of heterogeneity in tumor response to drugs that does not exist in vitro. **Therefore, prediction of drug effects in cancer patients based solely on in vitro data is not reliable and further evaluation in animal tumor systems is essential**." Zips et. al. "New Anticancer Agents: In Vitro and In Vivo Evaluation" in vivo 2005, 19, 1-8.

As for in vivo models it is known that a retrospective National Cancer Institute Study examined 39 drugs using transplantable human tumor cell lines and compared them to phase II clinical outcomes. (See Johnson, et. al. "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials." British Journal of Cancer 2001, 84, 1424-1431.) The in vivo xenograft data was not predictive of activity against the same human tumors, displaying the unpredictability of correlation and predictive value of the in vivo models.

This unpredictability is also apparent in regards to caspase inhibitors for cancer as follows:

The state of the prior art addresses the wide unpredictability of caspase inhibitors which is highly variable to the specific inhibitor (e.g. BCNU verses Z-VAD.FMK), the amount used, the specific combinations of components particularly with which anti-cancer agent, the cell line, and the type of cancer can result in substantially different results.

Slee et al. (Benzyloxycarbonyl-Val-Ala-Asp…) teaches the use of Z-VAD.FMK which inhibits apoptosis (cell death) by inhibiting the processing of CPP32 (pro-caspase-3) to its active form. Slee also teaches the Z-VAD.FMK was effective in inhibiting apoptosis in THP.1 cell, but Ac-DEVD-CHO and Ac-YVAD-CHO were not effective in inhibiting apoptosis, despite the fact that Ac-DEVD-CHO is an inhibitor of caspase-3.

However, Kim et al. teaches that Ac-DEVD-CHO attenuated indomethacin-induced DNA fragmentation (apoptosis) in colon cancer cells. Wherein Ac-DEVD-CHO was not effective with THP.1 cells and cycloheximide, it was with indomethacin and colon cancer cells.

Petak et al. teaches that BCNU is a caspase-mediated inhibitor and an anticancer agent. Petak teaches that BCNU is bifunctional and has the capacity to inhibit drug-induced apoptosis from etoposide at certain noncytotoxic doses (12-50um). The effects of inhibition were dependent on the dose of BCNU. BCNU is an alkylating nitrosourea derivative (mustard derivative). As a result, Petak teaches that the dose of amount as well as the specific inhibitor can directly affect the role and inhibition of the

agent. Petak also teaches that the fact a cytostatic agent in a dose that is noncytotoxic can eliminate or reduce the biological activity of another drug used in combination therapy can influence the clinical response.

Koken et al. (WO 00/07616- it is noted that U.S. Pat. No. 7217413 will be used as the translation and the references are to the U.S. Pat.) teaches that inhibitors of caspases, particularly zVAD (N-benzyloxycarbonyl-valyl-alanyl-aspartyl-fluoromethylketone) are involved in the apoptosis process and inhibition of certain caspases inhibit apoptosis, but that studies had shown that inhibitors associated with PML protein such as zVAD prevented or greatly inhibited cell death (apoptosis) . However, Koken et al. taught that zVAD did not inhibit apoptosis induced by interferon (anti-cancer agent-see Horrobin), which was contrary to expectation and actually accelerated the apoptosis (Abstract, Col. 1 lines 1-8 and 44-Col 2 line 22, Claim 1-8). Koken also applies zVAD with etoposide in testing and showed that zVAD had blocked the apoptosis induced by etoposide which is contrary to the instant claims as goes to the enablement and the unpredictability of the art.

Thereby, not all caspase inhibitors are effective in killing cancer cells, inhibiting the growth of cancer cells, and thereby treating cancer. Variables such as the particular caspase inhibitor, not just the type of caspase inhibitor (e.g. Ac-DEVD-CHO, not generally caspase-3 inhibitors, see all references above), whether in combination and what specifically it is combination with (Slee, Kim, Koken), the type of cancer (Slee, Kim), and the amount (Petak) will directly affect the outcome.

Thereby, due to the high unpredictability of the art and the wide range of possible effects that are divergent dependent of the factors addressed above, the generic use of a caspase inhibitor or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent would not be enabled for treating all cancers.

(5) The relative skill of those in the art:

One of ordinary skill is a medical doctor or Pharm. D. typically in oncology.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has only provided guidance for combining BCNU with caspase inhibitors for killing tumor cells in the examples on pages 35-36 and the description of the drawing of figures 1-7 on pages 2-4.

However, the specification **does not provide any disclosure** as to which specific inhibitors were utilized in the examples which as addressed above are critical to the outcome of treating cancer. For example, the specification only states the use of a pan caspase inhibitor but does not disclose anywhere in the drawings or examples which specific pan caspase inhibitors was used with the BCNU which as demonstrated by the art, is critical to the outcome as different compounds will produce different results with different cell lines, amounts, and drug combinations.

The specification does not provide what the amounts of BCNU are utilized in each example represented in the figures. As addressed above by Petak, the amount of BCNU is critical to the outcome of treatment. It also goes to the role of BCNU as if it is within the ranges of non-cytotoxic doses, it is acting as a caspase inhibitor. It is also a

question as to how to use BCNU as disclosed as a non-caspase inhibitor anti-cancer agent particularly an alkylating agent, when it is known in the art to possess caspase inhibition properties.

The specification utilizes 1789 glioblastoma, UT-9 and 12 astrocytoma, and SW480 colon cancer cell lines in the examples which as addressed above are not representative of all cancers and the type of cancer cell line and the agents used will yield various results. Additionally as addressed above with Trisha Gura, the cell line data for cancer drugs is well-known to be unpredictive of treatment in a patient as encompassed by the claims.

The lack of disclosure does not allow one of skill in the art duplicate the examples nor to make and use the invention.

The art only provides guidance for (1) caspase inhibitors associated with PML protein such as zVAD and/or arsenic compounds for inducing and/or accelerated cell death for undesirable cells and/or with an agent inducing the overexpression of the PML protein such as interferon (Koken et al.); and (2) method of inhibiting cancer cell proliferation with certain aminoiminoquinone and aminoquinone alkaloid compounds that can be in combination with other agents (Gunasekera et al.) which are addressed in detail in the art rejections below.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the enablement for the methods of treatment, the lack of

disclosure and guidance in the specification, and the high unpredictability in the art as evidenced therein, it is very clear that one could not make/use this very broad invention with no disclosure of the compounds utilized in the cell line examples in this unpredictable art without undue experimentation.

12. Claim 45-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims recited glutathione prodrugs wherein the specification does not reasonably provide enablement for prodrug forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There is no process enabling such a scope in the specification as it is nonlimiting as its not even described what type is suitable to practice the invention much less how to make and use a representative class. Applicants provide no reasonable assurance which if any prodrugs will have the ability to regenerate in vivo to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular prodrug form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing in vivo.

Pursuant to In re Wands, 8 USPQ2d 1400, factors such as:

(1) The nature of the invention and (2) the breadth of the claims:

The claim is drawn to glutathione prodrugs where the specification does not reasonably provide enablement for these forms. The breadth of the claims results in a scope of compounds that is easily in the millions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art addresses that formations of prodrugs are difficult, unpredictable, and variable. With regard to predictability, note Burger, provided with this action which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.976. Also, see Banker provided with this action, who in the first sentence of the 3rd paragraph on p.596 states that "extensive development must be undertaken to find the correct chemical modification for a specific drug." Additionally, Testa which is provided in the action, states the challenge of the biological variety results not just from the “huge number and evolutionary diversity of enzymes” involved in metabolism which may “render prodrug optimization difficult to predict and achieve” (Page 2098, Challenges in prodrug research). Thereby resulting in high unpredictability in the art.

(5) The relative skill of those in the art:

The degree of skill in the art is high, typically one with a Ph.D. in Chemistry.

6) direction or guidance:

None is seen in the specification. Many functional groups (e.g. hydroxy, amino groups) present in drugs are capable at least in theory to being derivatized but determining what is a prodrug (and what is not) requires knowledge of an intended

effect (i.e. modification of an undesirable property in the parent drug- poor solubility, poor bioavailability, poor shelf-life) which is never identified by the specification.;

7) presence or absence of working examples:

There is no example of a prodrug in the present case which does not allow one to ascertain the entirely of the claimed genus, the scope, nor how to make the genus claimed;

8) quantity of experimentation needed:

The amount of experimentation to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, note Burger, provided with this action which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.976. Also, see Banker provided with this action, who in the first sentence of the 3rd paragraph on p.596 states that "extensive development must be undertaken to find the correct chemical modification for a specific drug." Additionally, Testa which is provided in the action, states the challenge of the biological variety results not just from the “huge number and evolutionary diversity of enzymes” involved in metabolism which may “render prodrug optimization difficult to predict and achieve” (Page 2098, challenges in prodrug research). In view of all these factors undue experimentation would be required to practice the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 13-17, 38-49, 52-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite a non-caspase inhibitor which as defined in the specification does not have caspase inhibitory activity but cites DNA alkylating agents such as BCNU (carmustine) which is used in the examples and also claimed as a non-caspase inhibitor which is repugnant to the art as it conflicts with the teachings of Petak where *BCNU is caspase-inhibiting*. Whereby the examples presented are to caspase inhibitors and the claims encompass caspase inhibitors. It does not allow one of skill in the art to ascertain the metes and bound of the invention.

14. Claims 45 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite analogs of claimed antioxidants. This is indefinite as an analog can also be any number of things including a chemical analog and a functional analog. Dorland's Medical Dictionary cites that an analog (analogue) can be a chemical analog where it can be different is some aspect which is unclear as the specification does not describe what structural aspects must be present to be a chemical analog; and Dorland also cites that a compound may have similar or opposite metabolic action which is also unclear as the specification does not address what action is depicted for the analog or

to what degree to be quantified as an analog. It does not allow one of skill in the art to ascertain the metes and bounds of the invention. Clarification is requested.

The claims also recite vitamin E and tocopherol which are the same. It is unclear if it was intended to be a duplicate for the same component. It does not allow one of skill in the art to ascertain the metes and bounds of the invention.

The claims also recite multi-carotenes which is indefinite as it is unclear as to what encompasses multi-carotenes as the claims already cite the alpha, beta, and gamma-carotene forms. It does not allow one of skill in the art to ascertain the metes and bounds of the invention. Clarification is requested.

Claim Rejections - 35 USC § 102

The claims are so broad as to read upon the following pieces of art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 13-23, 38-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Koken et al. (WO 00/07616).

It is noted that U.S. Pat. No. 7217413 will be used as the translation and the references are to the U.S. Pat.

Koken et al. teaches that inhibitors of caspases are involved in the apoptosis process. Koken also teaches that certain combinations of caspase inhibitors and other agents including anti-cancer agents can result in improved apoptosis. An example is zVAD (N-benzyloxycarbonyl-valyl-alanyl-aspartyl-fluoromethylketone) where previous studies had shown that zVAD prevented or greatly inhibited cell death (apoptosis) . However, Koken et al. taught that zVAD did not inhibit apoptosis induced by interferon (interactive with tubulin-see Ginzburg et al.) and/or arsenic compounds such as arsenic trioxide (DNA fragmentation/strand-breakage agent: DNA interactive agent, see Trisenox-Mechanism of Action), but contrary to expectation accelerated the apoptosis. This was true to other inhibitors such as DEVD. Examples included fibroblasts and methods to ATL. Koken also applies zVAD with etoposide in testing and showed that zVAD had blocked the apoptosis induced by etoposide which are the same steps in the claims but contrary to the claimed therapeutic result of instant claims which goes to the enablement rejection and the unpredictability of the art as addressed above (Abstract, Col. 1 lines 1-8 and 44-Col 2 line 22, Col. 3 lines 1- Col. 4 line 55, Col. 9 line 30-col. 10 line 25, Claim 1-8, Figure 1-C, Example 3).

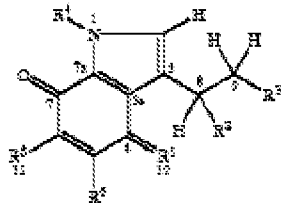
All the critical elements are taught by the cited reference and thus the claims are anticipated.

16. Claims 13-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Gunasekera et al. (U.S. Pat. 6218419).

Gunasekera et al. teaches the use of certain aminoiminoquinone and aminoquinone alkaloid compounds which are caspase inhibitors (e.g. CPP32-caspase

3) for treating cancer cells such as those for the colon, leukemia, and central nervous system (e.g. brain, gliomas). These compounds are

Compounds of the subject invention can be represented by the following general formula:



wherein R^1 is NH or O;
R^2 is OZ;
R^3 is OZ;
R^4 is H or R;
R^5 is NH_2, NR_2, or OZ; and
R^6 is H or X;

wherein Z is selected from the group consisting of H, R, COR, mesyl, tosyl, glutamyl, succinyl, and malonyl;

R is selected from the group consisting of C1 to C8 alkyl, phenyl, and benzyl; and

X is Cl, Br, or I.

Gunasekera teaches the use of these particular compounds for cancer treatment and the inhibition of cancer proliferation along with combination therapy with anti-cancer/immunomodulator agents including steroid anti-inflammatories/corticosteroids (Abstract, Col. 1 line 30-40, Col. 2 line 37-68, Col. 4 line 5-36, Example 9, Col. 15 line 52-Col. 16 line 11, Col. 16 line 30-68, Col. 17 line 1-39, Claim 16-22, 30).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 42-43 rejected under 35 U.S.C. 103(a) as being unpatentable over Gunasekera et al. (U.S. Pat. 6218419) as applied above, in view of Berg (Dexamethasone's new use in cancer treatment-Abstract).

The teachings of Gunasekera are addressed above.

Gunasekera does not expressly teach dexamethasone, methylprednisolone, prednisolone, or prednisone for treatment. Gunasekera does teach the use of corticosteroids for combination treatment with the taught compounds.

Berg teaches that dexamethasone has been long known for cancer treatment for leukemia and brain cancer (Abstract).

It would be obvious to one of skill in the art at the time of the invention to use dexamethasone for the treatment as it is known for use for the cancers taught by Gunasekera, Gunasekera teaches combination therapy with steroids, and it is obvious to combine two components each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose as Gunasekera already teaches the combination therapy.

One of skill in the art would be motivated to combine a well known steroid for its known use with the compounds of Gunasekera, also known for the same use as it is desirable to have and produce a composition comprising many components which have desirable effects for the condition resulting in the additive effect of the ingredients for treatment.

18. Claim 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gunasekera et al. (U.S. Pat. 6218419) as applied above, in view of Prasad et al. (High

Doses of Multiple Antioxidant Vitamins: Essential Ingredients in Improving the Efficacy of Standard Cancer Therapy).

The teachings of Gunasekera are addressed above.

Gunasekera does not expressly teach antioxidants for treatment. Gunasekera does teach the inclusion of other agents for combination treatment with the taught compounds.

Prasad teaches that antioxidant vitamins such as retinoids, ascorbic acid, tocopherol and carotenoid have anti-cancer properties and certain antioxidants at particular dosages/combinations can enhance the efficacy of standard tumor therapeutic agents in cancers such as neuroblastoma and colon. Recommended dosages are also taught.

It would be obvious to one of skill in the art at the time of the invention to use antioxidants such as tocopherols and ascorbics for use for the cancers taught by Gunasekera, as Gunasekera teaches combination therapy with steroids, Prasad teaches that they are useful and can enhance the efficacy of therapeutic cancer agents, wherein it is obvious to try and combine two components each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose as Gunasekera already teaches the combination therapy.

One of skill in the art would be motivated to combine antioxidants with the compounds of Gunasekera, both known for cancer treatment for increased additive results and increased efficacy, as it is desirable to have and produce a composition

comprising many components which have desirable effects for the condition for treatment.

Response to Arguments

19. Claims 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in regards to the terms “caspase inhibitor” and an inhibitor that is a “pan caspase inhibitor”, an inhibitor “specific for caspase-3, caspase-8, or caspase -9”, and wherein the caspase inhibitor “inhibits the production of a caspase" or “inhibits the activation of a caspase” or inhibits a signaling pathway of a caspase".

Applicant's arguments filed 12/9/2008 have been fully considered but they are not persuasive. Applicant asserts that the a number of caspase inhibitors are known and that one of skill in the art would be able to identify new caspase inhibitors through screen the compound using known assays. This is reinforces the issue of written description as Applicant is to be in possession of compounds useful for the method at the time of filing and identification of new compounds after the time of filing utilizing the assays after the time of filing directly goes Applicant not being in possession of those compounds at filing. Additionally, it is not sufficient to assay compounds for inhibitory activity as the claims require that they have the ability to inhibit the growth or kill of the cancer cell and many inhibitors are known to delay apoptosis which is contrary to the claimed method. As a result, Applicant is to have written description for the inhibitors useful for the method at the time of filing (e.g. structure/function relationship).

Applicant argues that there are examples demonstrating the enhanced apoptosis of glioblastoma and astrocytoma cell line with BCNU or Cisplatin with caspase-3, caspase-9, and a caspase-8/9 inhibitor, that one of skill in the art would be aware of the structural functional properties of the inhibitor and be able to screen for new compounds satisfying written description. This is not persuasive as while there are examples, there is no disclosure as to which caspase-3, caspase-9, and caspase-8/9 inhibitors were used. There is no disclosure in the examples, the figures, nor the description of the drawings of which ones were used to even ascertain the structure of the inhibitors in the examples to support the assert of the structure function relationship asserted by Applicant. Additionally, Applicant names BCNU as a non-caspase inhibitor which is repugnant to the art as it is a caspase inhibitor and is contrary to Applicant's definition in the specification which goes to the issue of written description for the terms, written description commensurate to the scope of the claim, and other 112 issues addressed above. This also leads to the issue of making and using the invention as addressed in the enablement rejection above and below.

Accordingly, the rejection is maintained.

20. Claims 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicant's arguments filed 12/9/2008 have been fully considered but they are not persuasive. Applicant asserts that examples demonstrated effective apoptosis with different caspase inhibitors with BCNU and cisplatin for glioblastoma and astrocytoma cell lines And that there is an overlap in treatment approaches where treatment of one

type of tumor is also used in the treatment for other cancers such that one of skill in the art would be able to practice the claimed invention with the three cancer cell types, the different caspase inhibitors and two anticancer agents in the examples. This is not persuasive as addressed above, the concept of a “silver bullet" for all cancers is contrary to what is known in oncology. Additionally, Applicant utilizes two cell lines that are directed to neuronal cells and one colon line which are not representative for all cancers. If fact, cell line data for cancer drugs is well-known to be unpredictive of treatment, even animal data is not predictive see Trisha Gura "where the cell line data is not reflective nor predictive for treatment in a patient in need thereof.

In regards to the examples as previously discussed, there is greater apoptosis but there is no means to make of use the invention nor even duplicate the examples as there is no disclosure as to which caspase-3, caspase-9, and a caspase-8/9 inhibitor were used by Applicant. What compounds where used is critical to the invention for enablement as the art is so highly unpredictable that the use of even two different caspase-3 inhibitors can result in the opposite effect as shown in the art (see Slee-one prevented cell death, one did not), or the type of cell line even with the same compound can result in different results (see Kim et al., Ac-DEVD-CHO attenuated indomethacin-induced DNA fragmentation (apoptosis) in colon cancer cells, but it was not effective with THP.1 cells and cycloheximide), and that the amount of drug can greatly change the action of the agent as addressed by Petak et al. who showed that BCNU is a caspase-mediated inhibitor and an anticancer agent, where it was bifunctional and has the capacity to inhibit drug-induced apoptosis (prevented cell death) from etoposide at

certain noncytotoxic doses (12-50um) which goes directly to the issues of the examples of the instant specification, 112 issues, and the claims. Petak teaches that effects of inhibition were dependent on the dose of BCNU and that the dose of amount as well as the specific inhibitor can directly affect the role and inhibition of the agent. Petak also teaches that the fact a cytostatic agent in a dose that is noncytotoxic can eliminate or reduce the biological activity of another drug used in combination therapy can influence the clinical response. Also, Koken shows that the same agent can behave completely differently depending in the combination- zVAD (caspase inhibitor) prevents cell death with etoposide but enhances cell death when with arsenic compounds and/or interferon.

Accordingly, the rejection is maintained.

21. Claims 13-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Koken et al. (WO 00/07616).

Applicant's arguments filed 12/9/2008 have been fully considered but they are not persuasive. Applicant argues that the amendments of claims 13-15 exclude Koken which is not persuasive as interferons are interactive with tubulin (see Ginzburg et al.) and/or arsenic compounds such as arsenic trioxide (DNA fragmentation/strand-breakage agent: DNA interactive agent, see Trisenox-Mechanism of Action). Additionally, Koken also applies zVAD with etoposide in testing and showed that zVAD had blocked the apoptosis induced by etoposide which are the same steps in the claims but contrary to the claimed therapeutic result of instant claims which goes to the enablement rejection and the unpredictability of the art as addressed above. As for Applicant's arguments that the recitation of "consisting essentially of" and the

amendments of claim 16 exclude Koken, this is not persuasive as the components of Koken do not materially change the composition use as they are utilized to treat the same condition. As for the claim 16 amendment, this is not persuasive as the argument is not commensurate in scope with the claim, the amendments are functional language, and the claim recite "comprising" language wherein it is still open to the inclusion of other components where Koken still applies.

Accordingly, the rejection is maintained.

Conclusion

22. Claims 13-23, 38-49, 52-53 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612